REMARKS

Status of the Claims

This amendment is further in response to the final Office Action, which issued on September 12, 2008. In addition to the amendment filed on March 12, 2009, the Examiner is respectfully requested to enter and consider the amendment filed herewith.

Claims 1, 2, 19, and 21 are pending in the present application. Claims 20 and 22-45 were previously canceled. Claims 3 and 5-18 were canceled in the amendment submitted on March 12, 2009. Claim 4 is canceled herein. Claim 1 is amended without prejudice or disclaimer. Support for the amendment to claim 1 is described herein below. Claim 2 is redrafted in independent form. No new matter is added by way of these amendments. Reconsideration and entry is respectfully requested.

Substance of the Interview

The Examiner contacted Applicants' representative on March 17, 2009, to discuss an Examiner's amendment. Specifically, the Examiner stated that, to expedite prosecution, claim 1 should be amended to cancel the term "OH." The Examiner also stated that the term -N-alkyl should be replaced with –NH-alkyl. In addition, the Examiner suggested that claim 2 be redrafted in independent form to remove issues concerning an alleged lack of antecedent basis for some of the substituents at positions R^{7a} and R^{21a}.

Applicants' representative contacted the Examiner on March 23, 2009, to discuss additional amendments to claim 1. The additional amendments discussed with the Examiner on March 23, 2009, are submitted herein.

Amendments

Claim 1 is amended to cancel the term OH per the Examiner's recommendation. The term –N-alkyl has been replaced with the term –N,N-dialkyl. Support for –N,N-dialkyl is found throughout the specification as originally filed including, *e.g.*, on page 6, lines 14, 16, 23, 25 and 26. These sections specify that R^7 and R^{21} represent RC(=Y)-O-, wherein Y represents an oxygen atom and R represents $R^{N1}R^{N2}N\text{-}R^{M}$-, wherein R^M represents –CO-O- and R^{N1} and R^{N2},

which are the same or different and represent a C_1 to C_{22} alkyl group, which may have a substituent. Further support for this amendment is found on page 10 in the originally filed specification at lines 15 and 18-19, which specify that R, as discussed above, is $R^{aN1}R^{aN2}N$-CO-O, wherein R^{aN1} and R^{aN2} are the same or different and represent a C_1 to C_{22} alkyl group which may have a substituent. In addition, further support for this amendment is found on page 13, lines 5-6, *i.e.*, "the compound according to [original] claim 1, wherein R^{N1} and R^{N2}, the same or different, represent C_1 to C_6 alkyl." Support is also found on page 34, line 12, *i.e.* "N-N-dimethylcarbamoyloxy", *emphasis added.* Further support is found at the R^{21} position in the compound depicted on page 124 in the originally filed application. *See* Exhibit A.

Claim 1 is also amended to specify that R represents 4-alkyl-piperazin-1-yl in lieu of piperazinyl. Support for this amendment is found throughout the specification as originally filed including, *e.g.*, on page 13, lines 8-9, *i.e.* "[t]he compound according to claim 1., wherein ...R^{N1} and R^{N2} are bonded, a non-aromatic heterocyclic group" in combination with the left-most structure depicted on page 13, line 12 (left, bottom row of depicted structures). Support is also found on page 33, lines 22-24, which specifies "[t]he compound according to claim 2, wherein R^{7a} and/or R^{21a} represent $R^{a12}CO$-O, wherein R^{a12} represents a group selected from a group consisting of;" in combination with page 34, line 4, the left most structure. Applicants further note that, although a hydrogen atom is depicted at the 4-position of the piperazin ring on the above-described pages, the originally filed application supports a substituent on the piperazin ring that corresponds to an alkyl group, *see, e.g.*, page 52, in the application as originally filed at line 28. *See* Exhibit A.

Additional support is found for 4-alkyl-piperazin-1-yl on page 34, lines 10, and 16 , *i.e.* "4-methylpiperazin-1-yl." Further support is found at the R^7 position in the compound depicted on pages 115, 124, and 132 in the originally filed application. *See* Exhibit A.

CONCLUSION

In view of the above amendment and remarks Applicants believe the present application is in condition for allowance. Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Linda T. Parker, Reg. No. 46,046, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: MAR 26 2009

Respectfully submitted,

By _____

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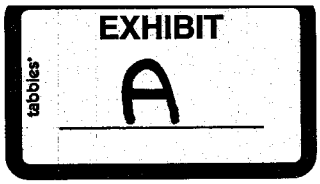


j) a C_6 to C_{14} aryloxy group which may have a substituent,

k) a C_3 to C_{14} cycloalkyl group which may have a substituent,

l) a 3-membered to 14-membered non-aromatic heterocyclic group which may have a substituent or

m) a 5-membered to 14-membered heteroaryloxy group which may have a substituent,

6) $R^{S1}R^{S2}R^{S3}SiO-$, wherein R^{S1}, R^{S2} and R^{S3}, the same or different, represent

a) a C_1 to C_6 alkyl group or

b) a C_6 to C_{14} aryl group,

7) a halogen atom,

8) $R^{N1}R^{N2}N-R^{M}-$, wherein R^{M} represents

a) a single bond,

b) $-CO-O-$,

c) $-SO_2-O-$,

d) $-CS-O-$ or

e) $-CO-NR^{N3}-$, wherein R^{N3} represents a hydrogen atom or a C_1 to C_6 alkyl group which may have a substituent, provided that, the leftmost bond in b) to e) is bonded to the nitrogen atom, and

-N,N-dialkyl

R^{N1} and R^{N2}, the same or different, represent

a) a hydrogen atom,

b) a C_1 to C_{22} alkyl group which may have a substituent,

c) an unsaturated C_2 to C_{22} alkyl group which may have a substituent,

e) a 5-membered to 14-membered heteroaryl group which may have a substituent,

f) a C_7 to C_{22} aralkyl group which may have a substituent,

g) a 5-membered to 14-membered heteroaralkyl group which may have a substituent,

h) a C_1 to C_{22} alkoxy group which may have a substituent,

i) an unsaturated C_2 to C_{22} alkoxy group which may have a substituent,

j) a C_6 to C_{14} aryloxy group which may have a substituent or

k) a 3-membered to 14-membered heteroaryloxy group which may have a substituent,

5) $R^{aN1}R^{aN2}N-CO-O-$, wherein R^{aN1} and R^{aN2}, the same or different, represent

-N,N-dialkyl

a) a hydrogen atom,

b) a C_1 to C_{22} alkyl group which may have a substituent,

c) an unsaturated C_2 to C_{22} alkyl group which may have a substituent,

d) a C_6 to C_{14} aryl group which may have a substituent,

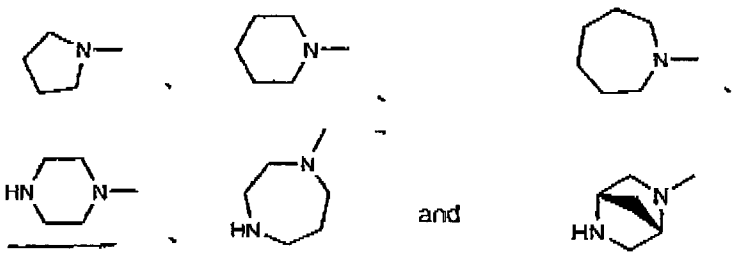
e) a 5-membered to 14-membered heteroaryl group which may have a substituent,

f) a C_7 to C_{22} aralkyl group which may have a substituent,

g) a 3-membered to 14-membered non-aromatic

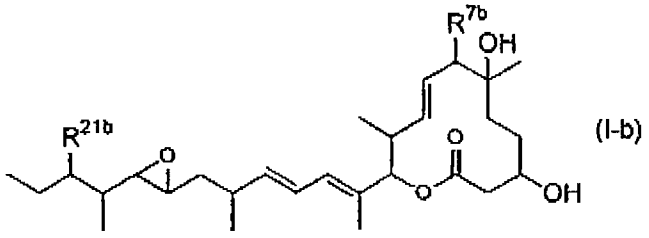
defined above, provided that, the leftmost bond in a) and b) is bonded to the nitrogen atom; or a pharmacologically acceptable salt thereof or a hydrate of those;

4. The compound according to 1., wherein R^{N1} and R^{N2}, the same or different, represent a C_1 to C_6 alkyl group or C_6 to C_{14} aryl group or form, together in combination with the nitrogen atom to which R^{N1} and R^{N2} are bonded, a non-aromatic heterocyclic group selected from the group consisting of:



or a pharmacologically acceptable salt thereof or a hydrate of those;

5. The compound according to 2. represented by the formula (I-b):



(I-b)

wherein R^{7b} and R^{21b}, the same or different, represent a C_1 to C_{22} aralkyloxy group which may have a substituent

5) a 5-membered to 14-membered heteroaryl group which may have a substituent,

6) a C_7 to C_{10} aralkyl group which may have a substituent,

7) a C_3 to C_8 cycloalkyl group which may have a substituent,

8) a C_4 to C_9 cycloalkylalkyl group which may have a substituent,

9) a 5-membered to 14-membered heteroaralkyl group which may have a substituent or

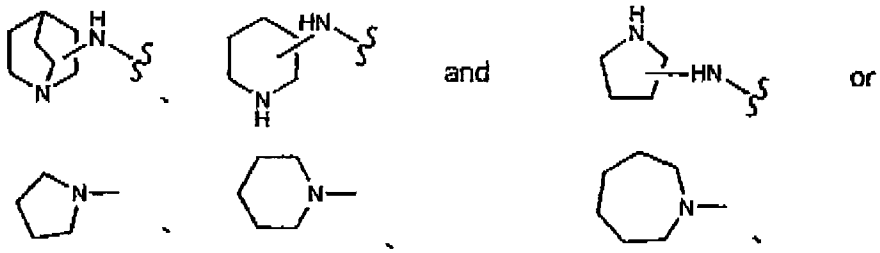
10) a 5-membered to 14-membered non-aromatic heterocyclic group which may have a substituent; or a pharmacologically acceptable salt thereof or a hydrate of those;

17. The compound according to 2., wherein R^{7a} and/or R^{21a} represent $R^{a11}CO-O-$, wherein R^{a11} represents a group of the formula (XIII):

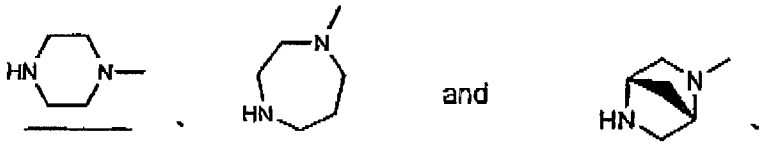
(XIII)

wherein m_5 represents an integer of 1 to 3, and n_5 represents 2 or 3; or a pharmacologically acceptable salt thereof or a hydrate of those;

18. The compound according to claim 2, wherein R^{7a} and/or R^{21a} represent $R^{a12}CO-O-$, wherein R^{a12} represents a group selected from a group consisting of:



or a group selected from a group consisting of



4-alkyl-piperazin-1-yl

and both of which may have a substituent on the ring; or a pharmacologically acceptable salt thereof or a hydrate of those;

19. The compound according to 1., which is (8E,12E,14E)-21-benzoyloxy-3,6-dihydroxy-6,10,12,16,20-pentamethyl-7-((4-methylpiperazin-1-yl)carbonyl)oxy-18,19-epoxytricosa-8,12,14-trien-11-olide, (8E,12E,14E)-21-(N,N-dimethylcarbamoyloxy)-3,6-dihydroxy-6,10,12,16,20-pentamethyl-7-((4-methylpiperazin-1-yl)carbonyl)oxy-18,19-epoxytricosa-8,12,14-trien-11-olide and (8E,12E,14E)-3,6-dihydroxy-6,10,12,16,20-pentamethyl-7-((4-methylpiperazin-1-yl)carbonyl)oxy-21-(N-phenylcarbamoyloxy)-18,19-epoxytricosa-8,12,14-trien-11-olide; or a pharmacologically acceptable salt thereof or a hydrate

N,N-dialkyl

4-alkyl-piperazin-1-yl

a group obtained by bonding a sulfinyl group to a terminal of the above-defined "C_1 to C_{22} alkyl group". Examples include a methylsulfinyl group, ethylsulfinyl group, n-propylsulfinyl group and iso-propylsulfinyl group. For example, a methylsulfinyl group and ethylsulfinyl group are preferable.

The "C_1 to C_{22} alkylsulfonyloxy group" used in the specification of the present application refers to a group obtained by bonding an oxygen atom to a terminal of the above-defined "C_1 to C_{22} alkylsulfonyl group". Examples include a methylsulfonyloxy group, ethylsulfonyloxy group, n-propylsulfonyloxy group and iso-propylsulfonyloxy group. For example, a methylsulfonyloxy group is preferable.

Given as the substituent in a group "which may have a substituent" used in the specification of the present application is one or more groups selected from:

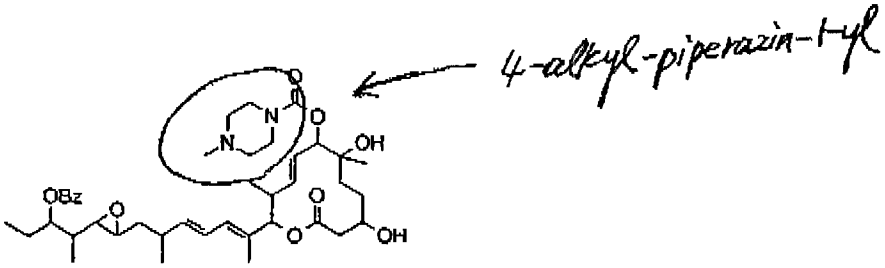
(1) a halogen atom,
(2) a hydroxyl group,
(3) a thiol group,
(4) a nitro group,
(5) a nitroso group,
(6) a cyano group,
(7) a carboxyl group,
(8) a hydroxysulfonyl group,
(9) an amino group,
(10) a C_1 to C_{22} alkyl group

a substituent on the 4-position of the piperazine ring

1.30 (1.8H, d, J=5.1Hz), 1.31 (1.2H, d, J=5.1Hz), 1.71 (3H, s), 2.30 (3H, s), 2.34-2.59 (8H, m), 2.59 (1H, dd, J=2.2, 7.7Hz), 2.73 (1H, dt, J=2.2, 5.9Hz), 3.44-3.65 (6H, m), 3.88-3.95 (1H, m), 4.90 (1H, d, J=10.6Hz), 4.95 (0.4H, d, J=9.5Hz), 4.96 (0.6H, d, J=9.5Hz), 5.04 (0.4H, q, J=5.1Hz), 5.12 (0.6H, q, J=5.1Hz), 5.18 (1H, dt, J=5.1, 7.0Hz), 5.56 (1H, dd, J=9.5, 15.0Hz), 5.57 (1H, dd, J=8.4, 15.0Hz), 5.75 (1H, dd, J=9.5, 15.0Hz), 6.06 (1H, d, J=11.0Hz), 6.28 (1H, dd, J=11.0, 15.0Hz), 7.45-7.52 (2H, m), 7.58-7.64 (1H, m), 7.98-8.04 (2H, m); ESI-MS m/z 711 $(M+H)^+$.

(Example 1-7 step)

(8E,12E,14E)-21-benzoyloxy-3,6-dihydroxy-6,10,12,16,20-pentamethyl-7-((4-methylpiperazin-1-yl)carbonyl)oxy-18,19-epoxytricosa-8,12,14-trien-11-olide (compound 1)

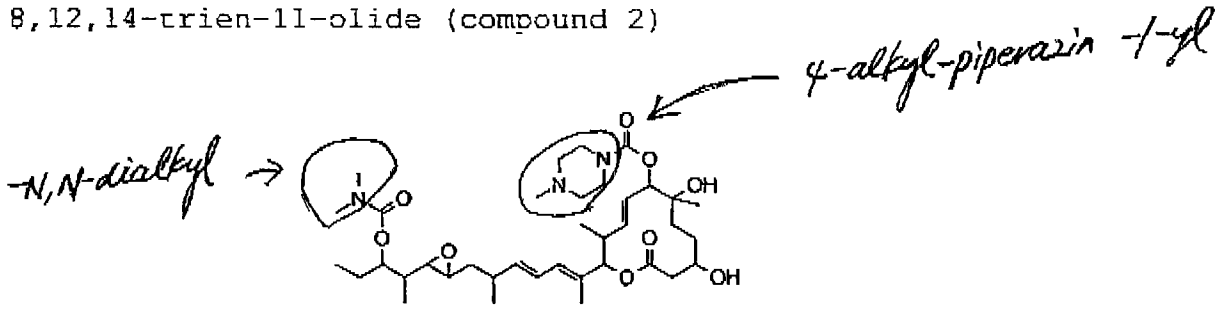


(8E,12E,14E)-21-benzoyloxy-6-(1-ethoxyethoxy)-6,10,12,16,20-pentamethyl-7-((4-methylpiperazin-1-yl)carbonyl)oxy-3-triethylsiloxy-18,19-epoxytricosa-8,12,14-trien-11-olide (19.7 mg, 21.6 μmol) was dissolved in methanol (1 mL). Pyridinium p-toluenesulfonate (12.2 mg, 48.5 μmol) was added to the reaction solution at room temperature, and the reaction solution was stirred at the same

0.90 (3H, d, J=7.3Hz), 0.98 (9H, t, J=8.1Hz), 1.07 (3H, d, J=7.0Hz), 1.15 (1.2H, t, J=7.0Hz), 1.17 (1.8H, t, J=7.0Hz), 1.290 (1.8H, s), 1.291 (1.8H, d, J=5.1Hz), 1.311 (1.2H, s), 1.312 (1.2H, d, J=5.1Hz), 1.39-1.73 (9H, m), 1.73 (3H, s), 2.29 (3H, s), 2.36-2.60 (8H, m), 2.56 (1H, dd, J=2.2, 7.7Hz), 2.71 (1H, dt, J=2.2, 5.9Hz), 2.90 (3H, brs), 2.92 (3H, brs), 3.40-3.66 (6H, m), 3.88-3.96 (1H, m), 4.75 (1H, dt, J=5.5, 7.3Hz), 4.91 (1H, d, J=10.6Hz), 4.94 (0.4H, d, J=9.9Hz), 4.95 (0.6H, d, J=9.9Hz), 5.04 (0.4H, q, J=5.1Hz), 5.12 (0.6H, q, J=5.1Hz), 5.56 (1H, dd, J=9.9, 15.4Hz), 5.65 (1H, dd, J=8.4, 15.0Hz), 5.75 (1H, dd, J=9.9, 15.4Hz), 6.09 (1H, d, J=11.0Hz), 6.31 (1H, dd, J=11.0, 15.0Hz); ESI-MS m/z 878 $(M+Na)^+$.

(Example 2-7 step)

(8E,12E,14E)-21-(N,N-dimethylcarbamoyloxy)-3,6-dihydroxy-6,10,12,16,20-pentamethyl-7-((4-methylpiperazin-1-yl)carbonyl)oxy-18,19-epoxytricosa-8,12,14-trien-11-olide (compound 2)

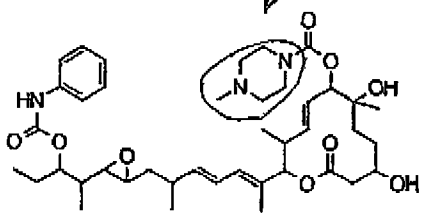


The title compound (colorless oil) was synthesized in the same manner as in the Example 1-7 step.

^{1}H-NMR Spectrum (CD_3OD, 400MHz) δ(ppm): 0.88 (3H, d,

11-olide (compound 3)

4-alkyl-piperazine-1-yl



The title compound (colorless oil) was synthesized in the same manner as in the Example 1-7 step.

^{1}H-NMR Spectrum (CD_3OD, 400MHz) δ(ppm): 0.87 (3H, d, J=7.0Hz), 0.93 (3H, d, J=7.3Hz), 0.94 (3H, t, J=7.3Hz), 1.04 (3H, d, J=7.0Hz), 1.20 (3H, s), 1.28-1.72 (9H, m), 1.72 (3H, s), 2.29 (3H, s), 2.51 (2H, d, J=3.7Hz), 2.37-2.60 (6H, m), 2.64 (1H, dd, J=2.2, 7.3Hz), 2.74 (1H, dt, J=2.2, 5.9Hz), 3.42-3.69 (4H, m), 3.73-3.80 (1H, m), 4.80-4.92 (1H, overlapped with H_2O), 4.92 (1H, d, J=9.5Hz), 5.03 (1H, d, J=10.6Hz), 5.56 (1H, dd, J=9.5, 15.4Hz), 5.60 (1H, dd, J=8.4, 15.4Hz), 5.70 (1H, dd, J=9.5, 15.4Hz), 6.06 (1H, d, J=11.0Hz), 6.28 (1H, dd, J=11.0, 15.4Hz), 7.00 (1H, dd, J=7.3, 7.3Hz), 7.26 (2H, dd, J=7.3, 8.1Hz), 7.42 (2H, d, J=8.1Hz); ESI-MS m/z 740 $(M+H)^+$.

INDUSTRIAL APPLICABILITY

According to the present invention, the compound of the formula (I) of the present invention inhibits, in particular, VEGF production and angiogenesis by altering gene expression, and exhibits